Case Report

NEPHRON

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Deliberate Overdose of Uranium: Toxicity and Treatment

Key Words
Uranium
Nephrotoxicity
Acute renal failure

Abstract

A case is described of deliberate ingestion of 15 g of uranium acetate which resulted in acute renal failure requiring dialytic therapy for 2 weeks, refractory anaemia, rhabdomyolysis, myocarditis, liver dysfunction with a disproportionate coagulopathy and paralytic ileus. Despite significant elevations in plasma uranium levels, treatment with both calcium EDTA and calcium DTPA were ineffective in promoting uranium excretion. Six months later the initial significant renal impairment exists with a persistent incomplete Fanconi syndrome. Future options for management of this unusual cause of acute renal failure are discussed.

Introduction

The acute and chronic exposure to chemical uranium is well known to manifest predominantly as nephrotoxicity [1, 2]. However, there are no reported cases of dialysis-requiring renal impairment following its ingestion. The majority of the literature addressing the toxicity of uranium arises from studies of addressing chronic exposure in the uranium industry [1–4]. Thus the clinical spectrum of toxic manifestations after acute exposure in humans is not well recognised, and as a consequence, guidelines for management of patients in this situation are not well established. We report a case of the deliberate ingestion of a stable uranium compound which resulted in significant systemic toxicity.

Case History

Mr. S.G. was admitted to Royal North Shore Hospital, Sydney, on the 28th October, 1993, following the deliberate ingestion of 15 g of uranium acetate and an unknown quantity of benzodiazepine.

His past history included established diagnoses of hyperlipidaemia, muscle enzyme deficiency, hypertension and hypogonadism. He also described having chronic peptic ulcer disease, asthma, gout, renal calculi, urinary tract infection and migraine. He admitted to self-medicating and abusing prescription drugs which he obtained from a number of medical practitioners for years. Until 1988 he was employed as an industrial pharmacist and during this time he obtained uranium acetate which he thought was radioactive. At the time of his admission he was dismissed from his research position in organic chemistry. The drugs he had regularly taken in the preceding 12 months included omeprazole, testosterone, cafergot, metaclopromide, cisapride, famotidine, cimetidine, ranitidine, misoprostil, mylanta, amitryptiline, simvastatin, panadeine forte, temazepam, topical agents, including various antifungals as well as steroid-based creams, and up to 4 different topical eye drops.

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He had a borderline personality disorder according to the criteria of DSM IIIR as well as narcissistic traits and episodes of depressed mood without biological symptoms. He had had psychotherapy on a regular basis for over 20 years. The breakup of his marriage, the loss of his home and dismissal from his research post led him to take uranium acetate in a calculated attempt to kill himself.

On admission to hospital it was established that he had ingested a stable uranium compound as his body and urine showed no traces of radioactivity. His initial management consisted of endotracheal intubation, nasogastric aspiration, which recovered a moderate amount of 'yellow cake', and subsequent lavage with 50 g activated charcoal. Intravenous fluids were administered, and he was extubated within 30 min. His examination then showed him to be drowsy with slurred speech, but oriented with no focal neurological deficit. He weighed 103 kg, his blood pressure was 150/100 and his pulse was regular at 100 beats per minute. He had mild bronchospasm evident, but his cardiovascular and gastrointestinal examinations were within normal limits.

His initial investigations were as follows: haemoglobin 13.6 g/dl, white cell count 18,000/mm^3, platelets 293,000/mm^3, sodium 142 mmol/l, potassium 4.4 mmol/l, chloride 109 mmol/l, bicarbonate 28 mmol/l, urea 3.2 mmol/l, creatinine 0.08 mmol/l. His liver function tests and his serum amylase were normal and his blood glucose level was 6.3 mmol/l. His arterial pH on no supplemental oxygen was 7.37, pO_2 95 mm Hg and pCO_2 38 mm Hg. His electrocardiograph demonstrated sinus tachycardia with a normal QT interval and normal ST segments. His urinary drug screen showed a trace of diazepam, and the panadol screen was negative.

The following day, some 16 h after admission, his urea was 7.8 mmol/l, and his creatinine was 0.27 mmol/l, at which time we reviewed the patient with respect to a nephrological opinion. His anion gap was 9 and his osmolar gap was 2. The repeat creatinine, using an enzymatic assay, was 0.33 mmol/l, the initial estimate having been performed on a Technicon autoanalyzer. His urinalysis was normal with a pH of 5, urine microscopy showed only red blood cells (following catheter insertion), creatinine kinase was 90 IU/l, urinary myoglobin was negative and renal ultrasound was normal, with in particular no evidence of urinary tract obstruction.

A diagnosis of acute nephrotoxicity due to heavy metal exposure was made. He was commenced on treatment with calcium ethylenediamine tetra-acetic acid (Ca EDTA), 1 g intravenously daily which was continued for 5 days, intravenous 8.4% sodium bicarbonate as required to maintain his urinary pH above 7 and mannitol to promote a diuresis. Despite these measures he became progressively oliguric (as shown in fig. 1), subsequently anuric and his creatinine rose to 0.89 mmol/l by day 4, at which time hemodialysis was instigated. The rate of rise in serum creatinine is depicted graphically in figure 2.

His course was further complicated by the development of paralytic ileus, persisting for 1 week from admission; rhabdomyolysis with a creatine kinase (confirmed to be a predominant MM subfraction) peaking at 8,418 IU/l on day 4; myocarditis complicated by symptomatic episodic atrial flutter controlled with digoxin; anaemia, with a fall in haemoglobin to 8.0 g/dl; liver dysfunction, with peak abnormalities detected at day 4 with an ALT of 192 IU/l, AST of 285 IU/l, GGT of 181 IU/l and albumin of 33 g/dl. A disproportionate coagulopathy was evident with an international normalized ratio (INR) of 2.5 and an activated partial thromboplastin time (APPT) of 50 s. Thyroid function tests were normal.

His plasma uranium, measured by mass spectrophotometry, on the day following commencement of chelation therapy was 3.24 µmol/l. Following 5 days of Ca EDTA, at which time he was on dialysis, his whole blood uranium level was 3.29 µmol/l, plasma uranium was 1.18 µmol/l and dialysate uranium 0.05 µmol/l. Chelation treatment was thus ceased. He remained dialysis-dependent for 2 weeks following which his renal function had recovered sufficiently to withdraw dialysis. At this time his whole blood uranium was 1.07 µmol/l and his plasma uranium 0.85 µmol/l. He was treated for a further 5 days with 1 g Ca EDTA daily, which resulted in the following urinary uranium excretions: day 1, 3.47 µmol/day, day 2, 2.51 µmol/day, day 4, 2.01 µmol/day and day 5, 2.59 µmol/day. During his admission the principal aims of the Consultation-Liaison Psychiatry Unit were to contain his potential to discharge himself and cause further harm as well as to try to resolve some of the outstanding issues with regard to his family and his work. He was discharged 32 days after his initial presentation with ongoing psychiatric care.

His anaemia persisted with a haemoglobin between 7.5 and 8.0 g/dl and his creatinine stabilised at 0.25 mmol/l. There was evidence of an incomplete Fanconi syndrome, manifesting as a renal tubular acidosis, requiring 18.5 g of supplemental bicarbonate per day, glycosuria and phosphaturia. He was readmitted on the 21st December, 1993, for assessment of the value of ongoing chelation therapy. Urinary uranium, measured before and after 1 g of Ca EDTA, did not demonstrate any increase in measured excretion as shown in figure 3.

Over the next 8 weeks his anaemia persisted and his renal function failed to improve. As Ca EDTA was ineffective in removing his body uranium stores, a test chelation dose of 1 g calcium diethylenetriamine penta-acetic acid (Ca DTPA) was given with baseline and chelated urinary uranium measurements obtained. Again, this failed to significantly enhance urinary uranium excretion (fig. 3). No adverse effects during or following the infusion were observed. In particular, his creatinine following the Ca DTPA remained at 0.23 mmol/l.

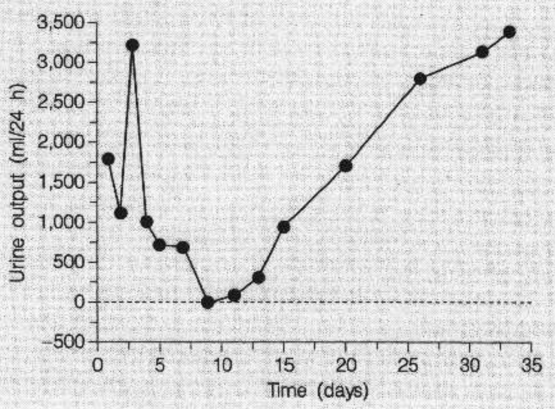
In a follow-up, now 6 months after the initial toxic insult, his creatinine has stabilised at 0.19 mmol/l. An incomplete Fanconi syndrome persists and he requires 20 g of supplemental sodium bicarbonate a day. His haemoglobin has improved to 11.8 g/dl and he has no residual manifestations of muscle, liver or cardiac toxicity.

Discussion

The case under discussion raises several interesting issues, particularly the somewhat unexpected spectrum of clinical toxicity including anaemia, liver dysfunction, myositis and myocarditis, and the lack of effective treatment for acute uranium toxicity beyond the immediate period of exposure. Despite the lack of literature regarding long-term sequelae following acute uranium exposure in human subjects, our case clearly illustrates that significant irreversible renal impairment occurs.

The chemical toxicity of uranium in the kidney is well demonstrated in both human and animal studies, and recommendations regarding limitations for exposure are based on considerations of its chemical toxicity rather than radioactivity [3]. However, acute renal failure due to uranium exposure is extremely uncommon. Uranium is poorly absorbed orally and estimated to be between 0.5 and 5% of the ingested dose in humans and various animal species [5–10]. The threshold for toxic damage is as low as 0.1 mg uranium/kg body weight entering the bloodstream [11, 12]. Thus the patient under discussion would only need have absorbed 0.07% of the ingested dose to cause clinical toxicity. In view of his history of gastrointestinal ulceration, it is likely that an impaired mucosal barrier aided absorption [10] and significantly increased his toxic insult.

The dominant toxicity observed was, as expected, primarily directed towards his kidneys. As was observed in this case, initial polyuria is a common feature of uranium toxicity [13], following which acute oligoanuric renal failure occurs. The uranyl ion is the most likely form of uranium to be present in body fluids following uranium exposure and in plasma, approximately 40% is bound to transferrin and 60% present as low molecular weight anionic complexes. The low molecular weight complexes are filtered at the glomerulus and dissociate as the pH falls along the tubule, freeing uranium to interact with luminal membrane proteins [1], which accounts for the dominant feature of renal tubular toxicity [1, 2]. Although a renal biopsy was not indicated in the case under discussion, it has been previously established that the tubular necrosis seen after uranyl nitrate administration begins in the pars recta proximal tubule at the corticomedullary junction and progresses proximally and distally to that site. The acute renal toxicity due to many of the heavy metals is often maximal within hours of injury and regeneration begins within 48 h of the acute insult. However, following uranium exposure, the injury is known to progress for up to 5 days [14]. In animal studies, regeneration of tubules may take up to 8 weeks at which time significant interstitial damage remains [15]. This longer toxicity is felt to reflect the fact that although 50% of circulating uranium will be excreted within 24 h, uranium can be deposited in the bone where it has a half-life variously estimated to be between 50 days and 7 years [16, 18], and can therefore be in equilibrium with the blood. Certainly the clinical manifestations of toxicity reflected a somewhat more prolonged exposure in this case and the plasma levels remained significantly elevated for at least 3 weeks following his ingestion, thus initially suggesting that effective chelation therapy may well have been a worthwhile therapeutic option.



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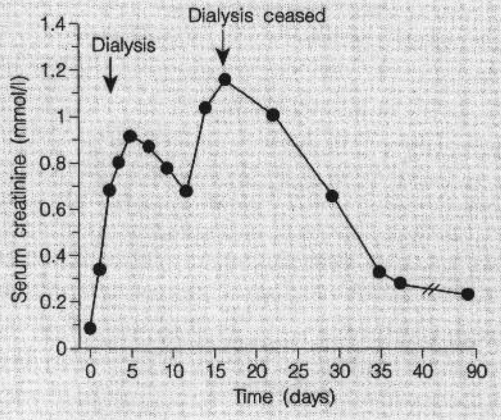

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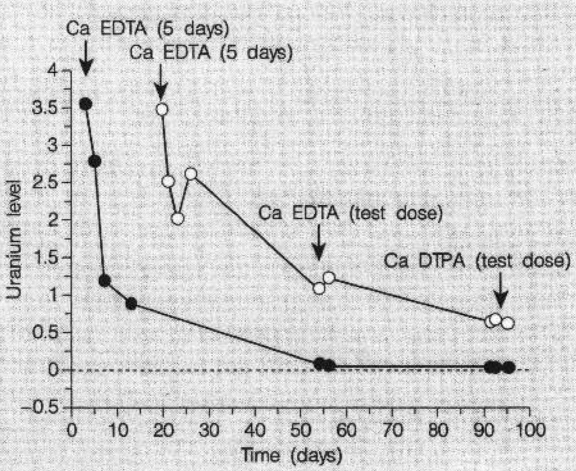

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Fig. 1. Urine output following clinical presentation.

Fig. 2. Serum creatinine (mmol/l) following clinical presentation.

Fig. 3. Plasma (●; μmol/l) and urinary (○; μmol/day) uranium excretion. Administration of Ca EDTA and Ca DTPA as indicated.

In contrast to the spectrum of toxicity exhibited by this patient, in experimental studies the chronic ingestion of oral uranium results in predominant deposition in kidney and bone [7, 10]. Localisation occurs to a lesser extent in thyroid and muscle [19], which probably accounts for the skeletal and myocardial toxicity observed in our patient. Although clinical evidence of liver toxicity and anaemia are rarely observed [19], postmortem studies have demonstrated a significant amount of uranium accumulation in the livers of occupationally exposed individuals [9, 20]. Furthermore, liver congestion has been observed to occur in up to 30% of rats treated with a high dose of uranium [19], which may well be the basis of the underlying liver pathology in the patient under review.

Therapy for acute chemical uranium exposure is limited. Few studies address the problem. However, there appears general agreement that for therapy to be effective it must be administered as soon as possible following exposure. In this case, the possibility of radioactive exposure appeared to overshadow the initial management of the patient, and the likelihood of heavy metal toxicity was not immediately considered.

Alkalinisation of the urine is known to increase urinary uranium excretion [18] as in an acidic urine the uranium dissociates from its bicarbonate complex and is then free to bind to the luminal aspect of the proximal tubular cells, promoting tubular toxicity as discussed above. An alkaline urinary pH was not achieved for at least 16 h after admission and up to 24 h after ingestion of the uranium. As the majority of circulating uranium would have been filtered by this time, it is likely that this therapy would have been more effective if initiated earlier.

Similarly, the effective elimination of uranium which had already been absorbed, would have no doubt been facilitated by the administration of a chelating agent within the first few hours of ingestion while the metallic ions are still in the circulation prior to incorporation into cells. Evidence exists that the combination of these two strategies, i.e. systemic infusion of bicarbonate and Ca EDTA, results in amelioration of renal damage [21]. Although it is impossible to speculate regarding the toxicity which would have occurred had our patient not received, albeit delayed, chelating therapy with Ca EDTA and urinary alkalinisation, it appeared not to confer a significant benefit on his clinical condition. Certainly Ca EDTA did not facilitate dialytic removal of uranium in the acute phases when significant elevations in plasma uranium were observed.

Although DTPA is generally more effective in chelating heavy metals [22], it is rarely used in clinical practice and availability limits its use in the acute setting, as occurred in the present instance. Despite there being nephrotoxic potential with both Ca EDTA and Ca DTPA [22], none was observed when these agents were administered when the patient was in the stable phase. However, in contrast with their effectiveness in removing tissue-bound lead [23], clearly neither agent was effective in removing body uranium stores in the doses given.

Although some work has been recently done on the synthesis of chelators for the uranyl ion [24] this appears to have little relevance to clinical application. Experimental data in mice [25] suggests that hexadentate TREN (Me-3,2-HOPO) [N,N′,N″-Tris-1,2-didehydro-3-hydroxy-1-methyl-2-oxopyrid-4-yl-(carbonyl)-2,2′,2″-triaminotriethyleneamine] is a more effective chelator of uranium compared to Ca DTPA when administered acutely, and suggests that significant reductions in body and kidney uranium may be achieved with treatment. Skeletal deposits of uranium are apparently inaccessible to the ligand, but more than half of the uranium circulating in plasma and extracellular fluid or loosely bound in soft tissue may be eliminated. However, there are no data concerning its efficacy in chronic toxicity and this agent is unlicensed for human use. Some evidence exists that ingestion of a mixture of Na_2HPO_4 and NaH_2PO_4 soon after oral ingestion of uranium results in an 80% reduction in systemic absorption of uranium [18]. However, this was not considered in our patient.

Thus, anecdotal evidence exists that acute treatment following uranium exposure directed towards facilitating excretion and limiting renal tissue binding may be beneficial in reducing toxicity. However, no studies support the use of either chelating agents or urinary alkalinisation beyond the immediate phase. Despite persistent elevations in plasma uranium levels, delayed therapy with both EDTA and DTPA were ineffective in promoting uranium excretion in the present case and significant renal impairment remains. The role of the newly developed chelating agents in these circumstances remains to be determined.

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References

1 Leggett RW: The behaviour and chemical toxicity of U in the kidney: A reassessment. Health Phys 1989;57:365–383.

2 Thun MJ, Baker DB, Steenland K, Smith AB, Halperin W, Berl T: Renal toxicity in uranium mill workers. Scand J Environ Health 1985;11: 83–90.

3 Kocher DC: Relationship between kidney burden and radiation dose from chronic ingestion of U: Implications for radiations standards for the public. Health Phys 1989;57:9–15.

4 Zhao SL, Zhao FY: Nephrotoxic limit and annual limit on intake for natural U: Health Phys 1990;58:619–623.

5 Hursh JB, Neuman WR, Toribara T, Wilson H: Oral infestion of uranium by man. Health Phys 1969;17:621–625.

6 Harrison JD: The gastrointestinal absorption of the actinide elements. Sci Total Environ 1991;100:43–60.

7 Tracy BL, Quinn JM, Lahey J, Gilman AP, Mancuso K, Yagminas AP, Villeneuve DC: Absorption and retention of uranium from drinking water by rats and rabbits. Health Phys 1992;62:65–73.

8 Wrenn ME, Singh NP, Ruth H, Rallison ML, Burleigh DP: Gastrointestinal absorption of soluble uranium from drinking water by man. Radiat Prot Dosim 1989;26:119–122.

9 Wrenn ME, Durbin PW, Howard B, Lipsztein J, Rundo J, Still ET, Willis DL: Metabolism of ingested U and Ra. Health Phys 1985;48:601–633.

10 La Touche YD, Willis DL, Dawydiak OI: Absorption and biokinetics of U in rats following an oral administration of uranyl nitrate solution. Health Phys 1987;53:147–162.

11 Yuile CL: Animal experiments; in Hodge HC, Stannard JN, Hursh JB (eds): Handbook of Experimental Pharmacology. Berlin, Springer, 1973, vol 36, pp 165–196.

12 Hursh JB, Spoor NL: Data on man; in Hodge HC, Stannard JN, Hursh JB (eds): Handbook of Experimental Pharmacology. Berlin, Springer, 1973, vol 36, pp 197–239.

13 Hodge HC: A history of uranium poisoning (1824–1942); in Hodge HC, Stannard JN, Hursh JB (eds): Handbook of Experimental Pharmacology. Berlin, Springer, 1973, vol 36, pp 5–68.

14 Haley DP: Morphologic changes in uranyl nitrate induced acute renal failure in saline and water drinking rats. Lab Invest 1982;46:196–208.

15 Haley DP, Bulger RE, Dobyan DC: The long term effects of uranyl nitrate on the structure and function of the rat kidney. Virchows Arch 1982;41:181–192.

16 Neuman WF, Fleming RW, Dounce AL, Carlson AB, O'Leary J, Mulryan B: The urinary excretion of citrate in uranium poisoned rats. J Biol Chem 1948;173:41–52.

17 Neuman WF, Newman MW, Main ER, Mulryan B: The deposition of uranium in bone, III. The effect of diet. J Biol Chem 1948;175:715–719.

18 Durbin PW, Wrenn ME: Metabolism and effects of uranium in animals; in Conference on Occupational Health Experience with Uranium. Washington, US Energy Research and Development Administration, 1976, pp 68–99.

19 Ortega A, Domingo JL, Llobet JM, Tomas JM, Paternain JL: Evaluation of the oral toxicity of uranium in a 4-week drinking-water study in rats. Bull Environ Contam Toxicol 1989;42: 935–941.

20 Kathren RL, McInroy JF, Moore RH, Dietert SE: Uranium in the tissues of an occupationally exposed individual. Health Phys 1989;57:17–21.

21 Dagirman Jian R, Maynard EA, Hodge HC: The effects of calcium disodium ethylenediaminetetraacetate on uranium poisoning in rats. J Pharmacol Exp Ther 1957;117:20–28.

22 Voelz GL: Current approaches to the management of internally contaminated persons; in The Medical Basis for Radiation Accident Preparedness. Elsevier, North Holland, 1980, pp 160–170.

23 CA Pollock, LS Ibels: Lead intoxication in Sydney Harbour Bridge workers. Aust NZ J Med 1988;18:46–52.

24 Franczyk TS, Czerwinski KR, Raymond KN: Stereognostic coordination chemistry. 1. The design and synthesis of chelators for the uranyl ion. J Am Chem Soc 1992;114:8138–8146.

25 Durbin PW, Kullgren B, Xu J, Raymond KN: In vivo chelation of Am (III), Pu (IV), Np (V) and U (VI) in mice by Tren-(Me-3,2-HOPO). Submitted for publication.